Turning Monoclonal Antibodies into Adenoviral Vectors - An Academic Perspective.

E.L. Berrie; E.J. Bolam; P. Bird; L. Andrews; P.A. Gallagher; C.A. Oliveira; P.G. Triggs and S.P. Moyle
Clinical BioManufacturing Facility, University of Oxford, Old Road, Headington, Oxford, OX3 7JT

The Clinical BioManufacturing Facility (CBF) has over 13 years experience producing biological Investigational Medicinal Products (IMPs) to EU GMP requirements. It was the first academic group to hold a MHRA manufacturing authorisation for IMPs. In October 2007, the CBF became the first UK University to manufacture an adenoviral vector. 75 volunteers have been immunised to date with three different CBF manufactured vectors and are currently in Phase I/IIb clinical trials. We have now manufactured four replication incompetent adenoviral vectors, utilising two chimpanzee backbones and one human backbone and three different transgenes. Further vectors are in process development, including a replication competent adenovirus.
The CBF originally opened in 1995 as the Therapeutic Antibody Centre (TAC) for pilot scale manufacture and testing of biological products. For 11 years, we produced monoclonal antibodies and related biologics that have been used worldwide to support more than 5,000 patients in clinical trials. With the maturing of monoclonal antibody manufacturing technologies, a decision was made to switch direction. We now support the next generation of unmet needs in 'proof of concept' clinical trials - manufacturing novel vaccines and gene therapeutics.
Upstream and downstream processing of monoclonal antibodies was based on generic methods. We hoped to use a similar strategy to manufacture adenoviral vectors. However, the uniqueness of each adenovirus has shown that an iterative approach is required, especially in downstream processing. The CBF team has adapted and learnt new skills to meet these challenges.
The CBF aims to provide the link between novel academic research and clinical drug development, working closely with and supporting collaborators to progress research products, through process development and manufacturing into the clinic.
A stopping point for most contract manufacturers is the release to trial of GMP material, which requires a Qualified Person. The CBF can release to trial, supporting sponsors from beginning to end (bench to bedside), including regulatory submissions.
The CBF has an established 'track record' to adapt to meet the needs of each project due to the persistence, ingenuity and broad skill base of staff from both academic, clinical research and biotech backgrounds.

In conclusion, the strength of the CBF is the ability to comply with the myriad of regulations surrounding GMP (Good Manufacturing Practice) and GCP (Good Clinical Practice) and consideration of academic needs when manufacturing IMPs for 'proof of concept' first in man trials; thereby enabling clinical research to advance.

Typical Virus Vector Production Process

Cell banking
↓
Virus banking
↓
GMP Manufacture
↓
Fill and finish
↓
QC testing
↓
QP final product release
↓
Clinical trial

Monoclonal Antibody Production

2009
- Fourth product is currently awaiting release to trial.
- Commencing the process of manufacturing the fifth product.
- Malaria challenge trial approved, immunisation began March 2009.
- Work with researchers on the process development in preparation for GMP manufacture (including a replication competent adenoviral vector).

2008
- Two adenoviral vectors manufactured and released to clinical trials.

2007
- February first adenoviral vector product filled released to clinical trial under *EMEA/CHMP/SWP/2836/07 Guidelines on strategies to identify and mitigate risks for first in human clinical trials with investigational medicinal products. Advanced Therapy Regulations, 2006/1296.*
- October first volunteer was immunised.

2006
- Validation of the hydrogen peroxide fumigation and building alterations were undertaken to redesign the air handling system, to enable the switch from manufacture of monoclonal antibodies to gene therapy products. These were done in order to satisfy the regulatory authorities.
- June, MHRA Authorisation, a change to the licence to encompass Gene Therapy Products, allowing adenoviral vector manufacture becoming the only UK University to carry out this process.
- July, the first vector transferred to the clean rooms for manufacturing the first Adenoviral Vector.
- Advanced Therapy Products Regulation 2006/1296 published.

2005
- November name changed to Clinical Biomanufacturing Facility to reflect the widening of the scope of production.
- The Clinical Biomanufacturing Facility integrated into the Nuffield Department of Clinical Medicine.

2004
- April received MHRA Manufacturing Authorisation. (Post UK Law Implementing the 'Clinical Trials Directive').
- Collaborative studies undertaken with TolerRx for CD3 and CD4 monoclonal antibodies.

2003
- GMP based Quality Management System finalised.

2002
- Planning for the implementation CTD under UK Law, TAC underwent a MHRA voluntary inspection . Millenium funding finished.

2001
- EU Clinical Trials Directive, 2001/20/EC. Campath was approved by the FDA for use in treating B-cell chronic lymphocytic leukaemia.

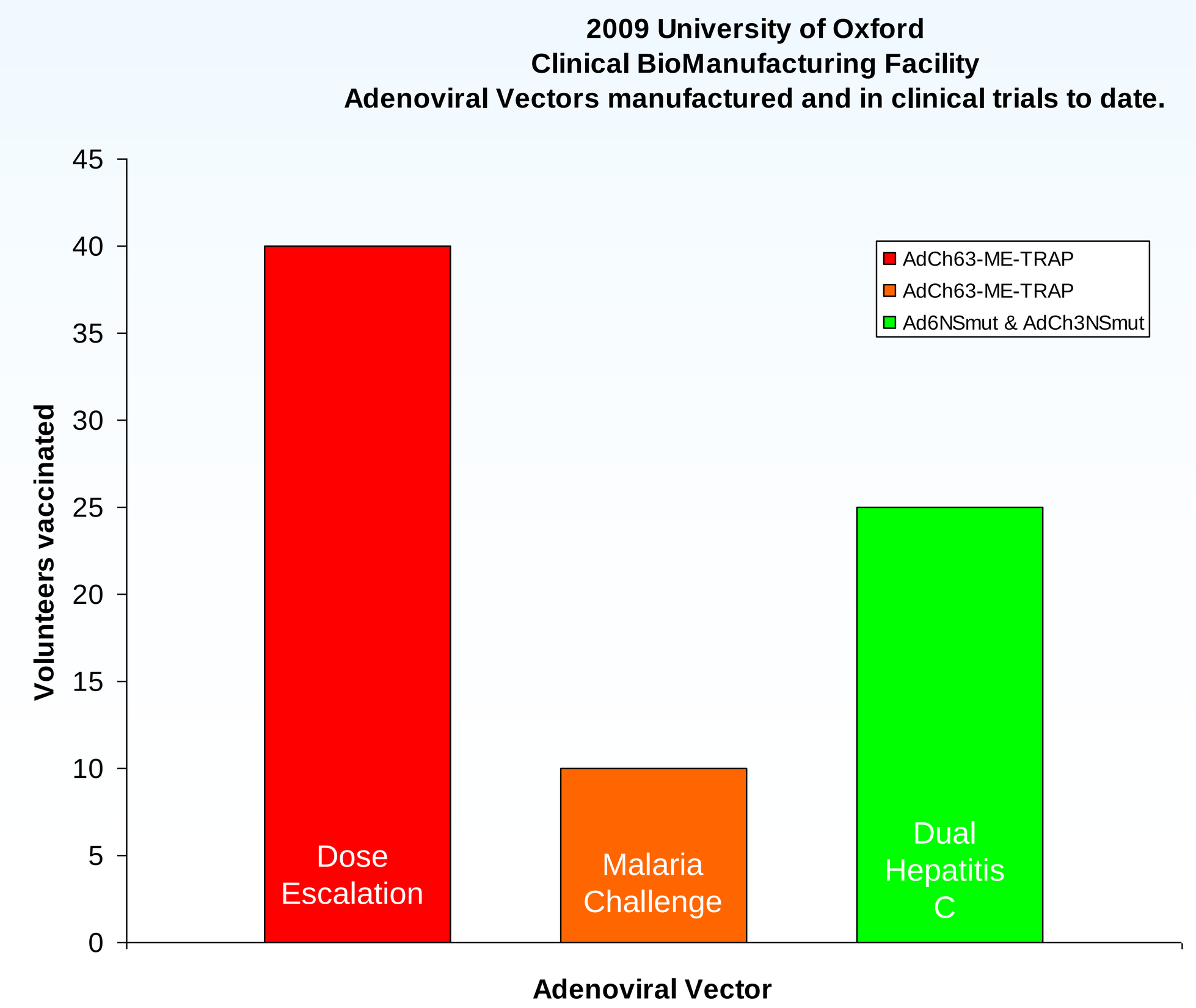
2000
- MRC Funding Ends Sept 2000.

1999
- Millenium Pharmaceuticals provides core funding for two rooms using standard operating procedures for use in clinical trials using the DDX system.

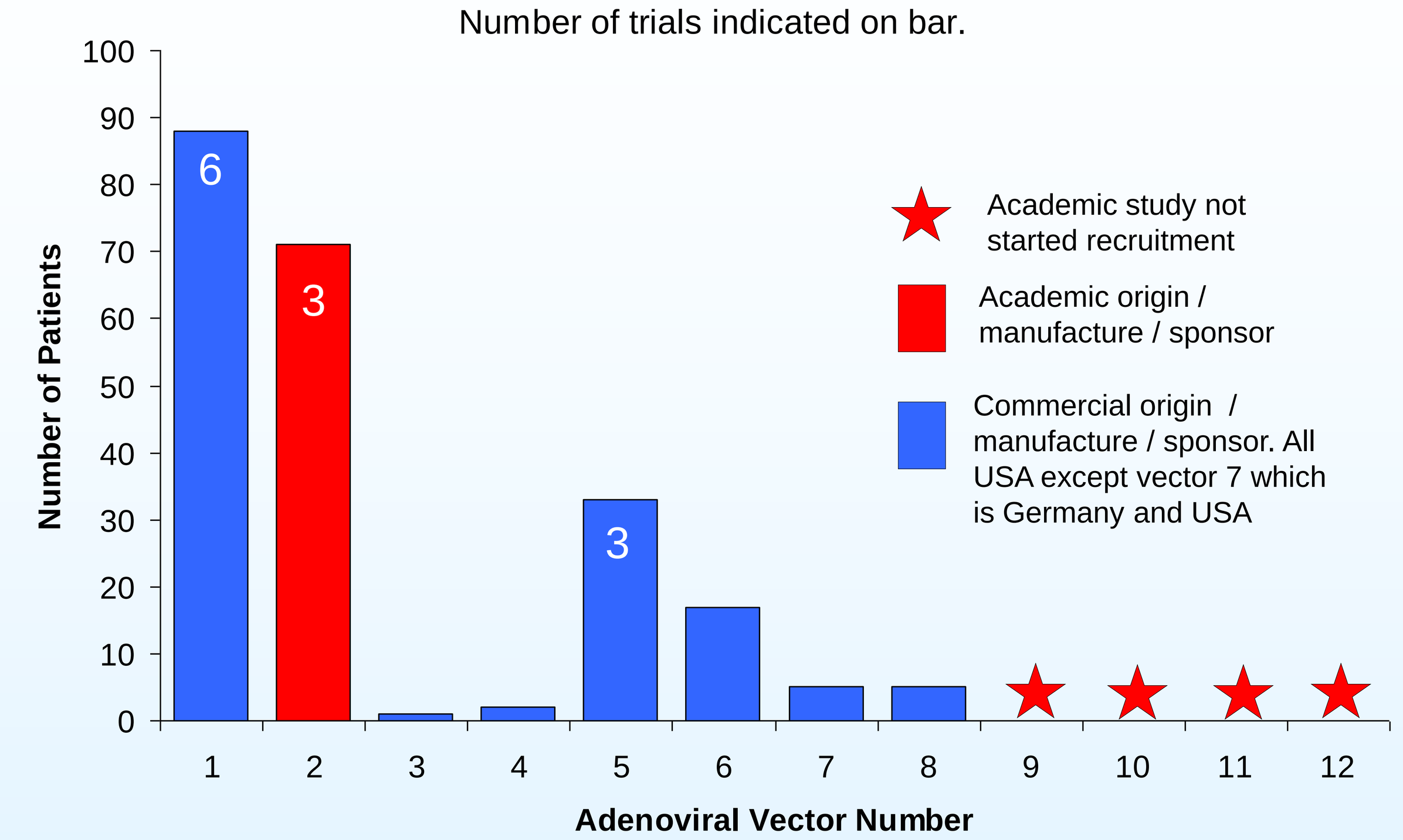
1995
- New Therapeutic Antibody Facility opens in Oxford. Funding for the new building and running expenses were granted by MRC and LeucoSite Inc. The Therapeutic Antibody Centre was established in order to provide a crucial link between the research effort of the scientists and the application of new concepts and products in the clinic. The role was to provide adequate quantities of therapeutic antibodies for pilot studies consistent with the best possible quality and safety. Whilst undertaking this work there was development of and improvement in the fermentation, purification and standardisation of techniques.

1990-1995
- Therapeutic Antibody Centre established by Professor Herman Waldman and Geoff Hale in Cambridge.

Adenoviral Vector production →



Number of subjects treated in all UK GTAC approved trials with same Adenoviral Vector. Information from GTAC 1993 - end 2007.
Number of trials indicated on bar.



Antibody production →

From 1995 to 2005 many different monoclonal antibodies and similar biologicals were manufactured by TAC, products included :

NHM	Glyco 1	ChAglyCD3
hIgG1 CD4	Glyco 2	TRX 1
FcRmut CD4	SM3	Campath 1H
FcRmut CD18	YTH 24.5	Campath 1M
TNFR-Ig	YTH 54.12	Campath 1G
CD4	YAML 568	Chi Lob 7/4
72A1		

The next stage →

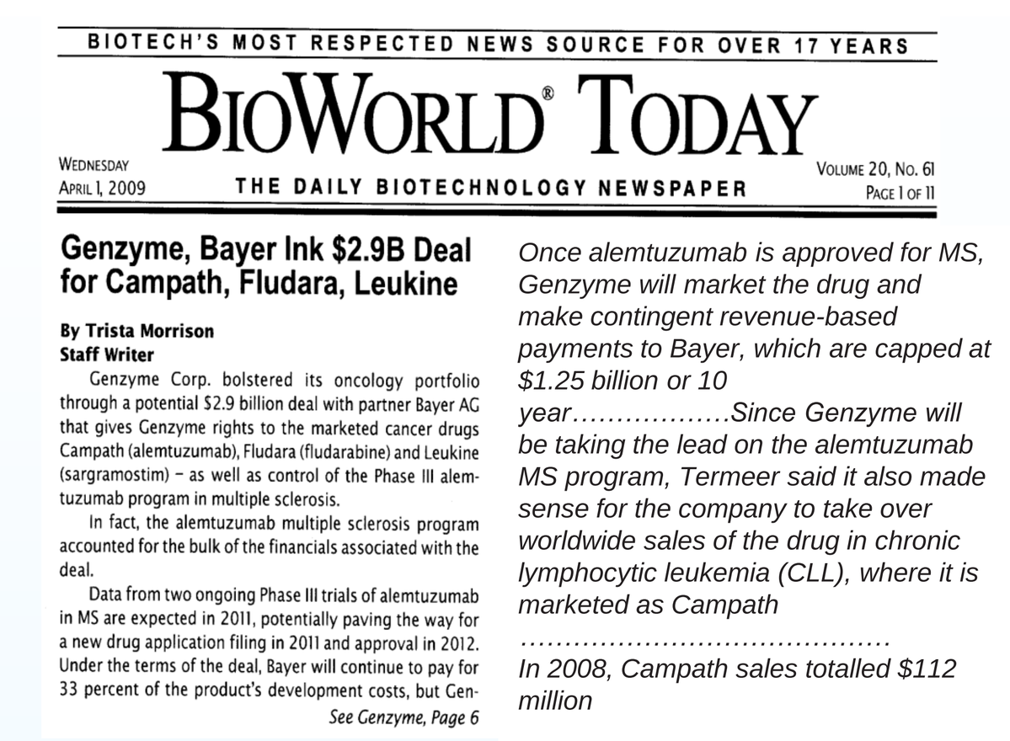
Malaria vaccine trials begin using 'chimpanzee virus'. *Trials are underway for a new vaccine to combat the most deadly form of malaria.*

University of Oxford
01.02.2008

'Malaria claims one life every 30 seconds'

So far, it has triggered an immune response against the malaria parasite in everyone tested by Oxford University researchers…………………………

Researcher Dr Sarah Gilbert said: " We're very excited by the results. If the vaccine works really well and is used in combination with drugs and methods like bed nets, malaria could be eradicated."


BIOTECH'S MOST RESPECTED NEWS SOURCE FOR OVER 17 YEARS
BIOWORLD® TODAY
THE DAILY BIOTECHNOLOGY NEWSPAPER
WEDNESDAY APRIL 1, 2009 VOLUME 20, NO. 61 PAGE 1 OF 11

Genzyme, Bayer Ink $2.9B Deal for Campath, Fludara, Leukine

By Trista Morrison
Staff Writer

Genzyme Corp. bolstered its oncology portfolio through a potential $2.9 billion deal with partner Bayer AG that gives Genzyme rights to the marketed cancer drugs Campath (alemtuzumab), Fludara (fludarabine) and Leukine (sargramostim) – as well as control of the Phase III alemtuzumab program in multiple sclerosis.

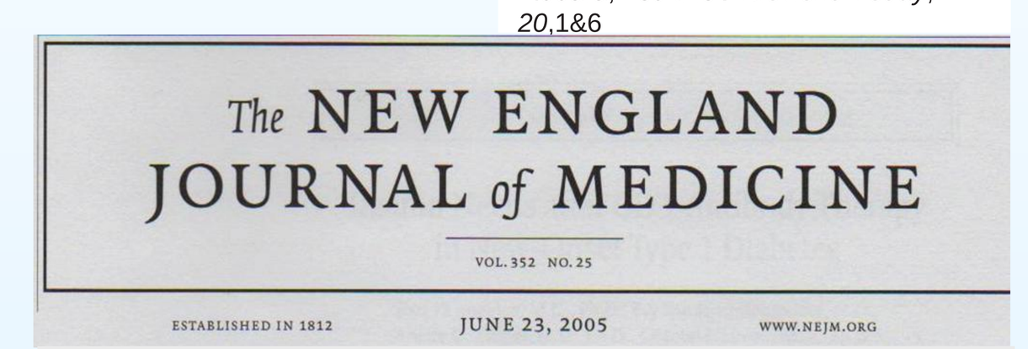
In fact, the alemtuzumab multiple sclerosis program accounted for the bulk of the financials associated with the deal.

Data from two ongoing Phase III trials of alemtuzumab in MS are expected in 2011, potentially paving the way for a new drug application filing in 2011 and approval in 2012. Under the terms of the deal, Bayer will continue to pay for 33 percent of the product's development costs, but Gen-

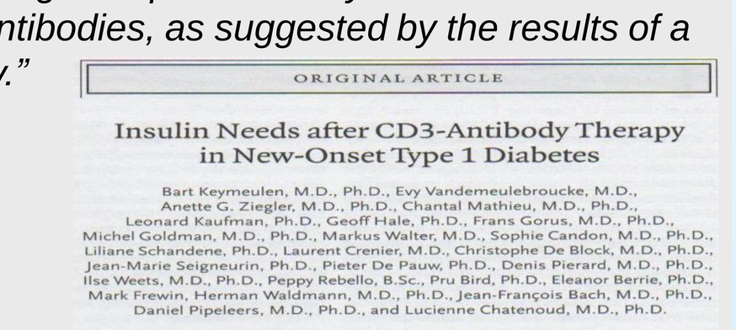
See Genzyme, Page 6

Once alemtuzumab is approved for MS, Genzyme will market the drug and make contingent revenue-based payments to Bayer, which are capped at $1.25 billion or 10 year………………Since Genzyme will be taking the lead on the alemtuzumab MS program, Termeer said it also made sense for the company to take over worldwide sales of the drug in chronic lymphocytic leukemia (CLL), where it is marketed as Campath ……………………………………
In 2008, Campath sales totalled $112 million

Ref: Trista Morrison. (2009).' Genzyme, Bayer Ink $2.9B deal for Campath, Fludara, Leukine'. *Bioworld Today*, *20*,1&6


The NEW ENGLAND JOURNAL of MEDICINE
VOL. 352 NO. 25
ESTABLISHED IN 1812 JUNE 23, 2005 WWW.NEJM.ORG

"*Type 1 diabetes is a T-cell- mediated autoimmune disease that leads to a major loss of insulin- secreting beta cells. The further decline of beta-cell function after clinical onset might be prevented by treatment with CD3 monoclonal antibodies, as suggested by the results of a phase 1 study.*"


ORIGINAL ARTICLE
Insulin Needs after CD3-Antibody Therapy in New-Onset Type 1 Diabetes
Bart Keymeulen, M.D., Ph.D., Evy Vandemeulebroucke, M.D., Anette G. Ziegler, M.D., Ph.D., Chantal Mathieu, M.D., Ph.D., Leonard Kaufman, Ph.D., Geoff Hale, Ph.D., Frans Gorus, M.D., Ph.D., Michel Goldman, M.D., Ph.D., Markus Walter, M.D., Sophie Candon, M.D., Ph.D., Liliane Schandene, Ph.D., Laurent Crenier, M.D., Christophe De Block, M.D., Ph.D., Jean-Marie Seigneurin, Ph.D., Pieter De Pauw, Ph.D., Denis Pierard, M.D., Ph.D., Ilse Weets, M.D., Ph.D., Peppy Rebello, B.Sc., Pru Bird, Ph.D., Eleanor Berrie, Ph.D., Mark Frewin, Herman Waldmann, M.D., Ph.D., Jean-François Bach, M.D., Ph.D., Daniel Pipeleers, M.D., Ph.D., and Lucienne Chatenoud, M.D., Ph.D.

Beyond clinical trials →

"Short- treatment with CD3 antibody preserves residual beta-cell function for at least 18 months in patients with recent onset type 1 diabetes."

Bart Keymeulen et al. (June 23,2005)*The NEW ENGLAND JOURNAL of MEDICINE 352 No.25 2598-2608*

ACKNOWLEDGEMENTS

All past and current TAC and CBF staff members with particular thanks to Prof. Geoff Hale and Prof. Herman Waldman. The CBF management committee; Prof. Adrian Hill; Prof Len Seymour; Dr. Tom Hanke; Dr Sarah Gilbert; Mr Gary Strickland; The Division of Medical Sciences and Colleagues of the Jenner Institute, University of Oxford; Okairòs; BRC and CR-UK.